Cited Document 2

# PATENT SPECIFICATION (11) 1 519 147

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(21) Application No. 42387/74 (22) Filed 30 Sept. 1974
(21) Application No. 1587/75 (22) Filed 14 Jan. 1975
(23) Complete Specification filed 30 Sept. 1975
(44) Complete Specification published 26 July 1978
(51) INT CL² C07C 43/22; A61K 27/00; C07C 49/32, 149/36
(52) Index at acceptance
C2C 1412 20Y 215 220 227 22Y 237 246 250 252 25Y 282 29X 29Y 305 30Y 313 31Y 320 321 322 323 32Y 338 342 34Y 360 361 364 366 367 368 36Y 373 37Y 38Y 396 397 451 45Y 464 465 490 503 50Y 583 613 620 623 624 628 62X 630 634 650 652 658 65X 662 699 703 774 775 777 790 79Y BX KQ LA LF QN QT RE RN WK WR

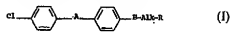

(72) Inventor VICTOR LAFON

## (54) SULPHUR- AND OXYGEN-CONTAINING DIARYL COMPOUNDS

(71) We, LABORATOIRE L. LAFON, a French Body Corporate, of 1 Rue Georges Mederic, 94, Maisons-Alfort, France, do hereby declare the invention for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to sulphur- and oxygen-containing diaryl compounds, their preparation and their application in therapy.

The present invention provides a diaryl compound of the general formula




(I)

in which one of A and B is O, S, SO or $SO_2$ and the other is O; Alk is a $C_1$—$C_4$ hydrocarbon radical with a straight or branched chain; R represents a group of formula COOX, wherein X is an esterified bis-[(S-hydroxyalkyl)thio]-alkane group, COOH in the form of its addition salt with a bis-[(N-hydroxyalkyl)amino-alkylthio]-alkane of the formula Bo-NRo-Ao-$SO_x$—$(CH_2)_n$—$SO_x$-Ao-NRo-Bo (IX), (wherein Bo is a $C_2$—$C_4$ hydroxyalkyl group or a $C_3$—$C_4$ dihydroxyalkyl group, Ao is a $C_2$—$C_4$ alkylene group, Ro is H, alkyl, acyl, or Bo, and x is 0, 1 or 2), OH, O—$SO_3CH_2$, $NH_2$, NHZOH, $NHZNR_1R_2$, C(=NH)$NH_2$, C(=NH)NHOH or 2-$\Delta^2$-imidazolinyl; Z is a $C_2$—$C_4$ hydrocarbon radical with a straight or branched chain; and $R_1$ and $R_2$ each represent a $C_1$—$C_4$ lower alkyl group, or together form, with the nitrogen atom to which they are linked, a N-heterocyclic group of 5 to 7 ring atoms which can be substituted and can comprise a second hetero-atom, and its addition salts with acids when R is a basic radical.

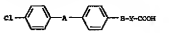
In the text which follows, the generic term "amidine" is to be understood to include not only the group C(=NH)$NH_2$ but also the amidoxime group C(=NH)NHOH and cyclic amidine groups such as the 2-$\Delta^2$-imidazolinyl group.

The ter "Alk" represents in particular the groups $CH_2$, $CH(CH_3)$, $C(CH_3)_2$, $CH_2CH_2$, $CH(CH_3)CH_2$, $C(CH_3)_2CH_2$, $CH_2CH(CH_3)$ or $CH_2C(CH_3)_2$. The group Z is in particular, $CH_2CH_2$, $CH(CH_3)CH_2$, $C(CH_3)_2CH_2$, $CH_2CH(CH_3)$ or $CH_2C(CH_3)_2$.

In the group COOX, X is an ester radical which results from the esterification of a bis-[(S-hydroxyalkylthio]-alkane as in British Specification No. 1,307,227.

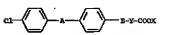
Among the N-heterocyclic groups $NR_1R_2$ included in the definition given above there may be mentioned the morpholino, pyrrolidino, piperidino, 4-methyl-piperidino, 4-methyl-piperazino, 4-*p*-chlorophenyl-piperazino and azepino groups. The preferred groups $NR_1R_2$ are the dimethylamino and diethylamino groups.

Preferred compounds according to the invention are:
a) the addition salts of acids of the formula:



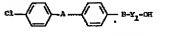
(Ia)

in which A is O, S, SO or $SO_2$, B is O, or S if A is O, Y is $CH_2$, $CH(CH_3)$ and $C(CH_3)_2$, with the bis-[(N-hydroxyalkyl)aminoalkylthio]-alkanes of the formula (IX) mentioned above;
b) the esters of the formula:



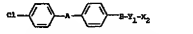
(Ib)

wherein A is O, S, SO or $SO_2$, B is O, or S if A is O, Y is $CH_2$, $CH(CH_3)$ and $C(CH_3)_2$ and X is as defined above;
c) the alcohols of the formula:



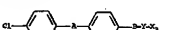
(Ic)

wherein A is O, S, SO or $SO_2$, B is O or S if A is O and $Y_1$ is $CH_2CH_2$, $CH(CH_3)CH_2$, $C(CH_3)_2CH_2$, $CH_2CH(CH_3)$ and $CH_2C(CH_3)_2$, and their derivatives resulting from the conversion of the OH group to an $O-SO_2CH_3$ group;
d) the amines of the formula:



(Id)

in which A is O, S, SO or $SO_2$, B is O or S if A is O, $Y_1$ is $CH_2CH_2$, $CH(CH_3)CH_2$, $C(CH_3)_2CH_2$, $CH_2CH(CH_3)$ or $CH_2C(CH_3)_2$, and $X_2$ is $NH_2$, $NHCH_2CH_2OH$, $NHCH(CH_3)CH_2OH$, $NHC(CH_3)_2CH_2OH$, $NHCH_2CH_2N(CH_3)_2$, $NHCH_2CH_2N(C_2H_5)_2$, and their acid addition salts; and
f) the amidines of the formula:



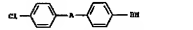
(Ie)

in which A is O, S, SO or $SO_2$, B is O or S if A is O, Y is $CH_2$, $CH(CH_3)$ and $C(CH_3)_2$ and $X_3$ is C(=NH)$NH_2$, C(=NH)NHOH and 2-imidazolinyl and their acid addition salts.

The compounds of the formula I may be prepared by the two methods described below with their variants, where appropriate.

*Method A*

A diphenyl derivative of the formula:



(II)

wherein A and B are defined as above, is reacted with a halogen derivative of the formula:

Hal-Alk-R′ (III)

wherein Hal is a bromine or chlorine atom and R′ is $COOC_2H_5$, OH, $NH_2$, NHZOH, $NHZNR_1R_2$, and CN, so as to give a compound of the formula:

(IV)

followed by
a) hydrolyzing a carboxylate (IV, R′=$COOC_2H_5$) to the corresponding acid (IV, R=COOH) which is then converted (by methods known *per se*) to said COOX

group or said addition salt of COOH, or is amidified and reduced to give an amine; or, followed by, if desired,

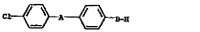
b) converting the alcohol (IV, R'=OH) to the corresponding mesylate (R=O—$SO_2CH_3$) by reaction with methane sulphonyl chloride; or

c) reacting a cyanide (IV, R'=CH) with $NH_3$, $NH_4OH$ and $H_2NCH_2CH_2NH_2$, in the presence of an alcohol to produce an amidino compound in which R is C(=NH)$NH_2$, C(=NH)NHOH or 2-$\Delta^2$-imidazolinyl, respectively.

To carry out the reaction II+III it is preferred to use a bromine derivative (III, Hal=Br) if R' is $COOC_2H_5$. Furthermore, if R' is CN, OH or amino, it is possible to use a chlorine or bromine derivative III, the chlorine derivative generally giving better yields than the bromine derivative in this case.

Amongst the variants of method A there may be mentioned:

A method for producing said addition salt of COOH by reacting a compound of the formula:

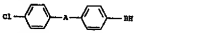


wherein A and B are as defined in claim 2, with a bromo compound of the formula:

$$Br—Y—COOC_2H_5$$

wherein Y is as defined in claim 2, hydrolysing the ester obtained, and converting (by methods known *per se*) the resulting acid to the specified addition salt of COOH;

A method for producing a compound or salt (Id) above by reacting a diphenyl derivative of the formula:



wherein A and B are as defined in claim 6, with a chloroalkylamine of the formula:

$$Cl—Y_1—X_2$$

wherein $Y_1$, and $X_2$ are as defined in claim 6;

the production of amines from alcohols or the mesylates (R=O—$SOCH_3$) of the latter;

the production of the COOX ester by transesterification of the compound IV (R'=$COOC_2H_5$);

the production of amides from the ester IV (R'=$COOC_2H_5$) by reaction with amines, or

the direct production of amides by reaction of II with a bromo-alkylamide of the formula III (R'=carboxamido), followed by reduction to an amine;

the production of the alcohol by reduction of the corresponding acid R=COOH;

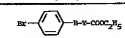
the oxidation of the sulphide group A=S to the sulphinyl group A=SO and to the sulphonyl group $A=SO_2$, by oxidation of the said sulphide by $H_2O_2$ in the presence of acetic acid; this oxidation is carried out in accordance with a method which is in itself known, and for this purpose it is recommended to carry out the reaction at a temperature below, or equal to, 50°C to obtain the sulphinyl derivative and at a temperature above 55°C (55°C to 100°C) to obtain the sulphonyl derivative, using concentrated hydrogen peroxide of at least 110 volumes strength (that is to say water containing at least 33% by weight of hydrogen peroxide); the oxidation by means of $H_2O_2$ can be carried out at any stage of method A.

*Method B*

Method B, which is less general than the preceding method, comprises the reaction of a cuprous salt of the formula:

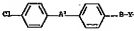
 (V)

wherein A' is O or S, with a bromine derivtive of the formula:



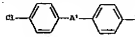
(VI)

in which B is O and can represent S if A' is O, and Y is $CH_2$, $CH(CH_3)$ or $C(CH_3)_2$ to give an ester of the formula:



(VII)

which is hydrolysed to give the corresponding acid



(VIII)

The acid of formula (VIII) is thereafter reacted as indicated for formula (IV) above, as appropriate.

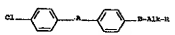
The addition salts with acids, which can be prepared from the bases of the formula I, are obtained by methods in themselves known, for example by reaction of the free base with an inorganic or organic acid. Amongst the acids which can be used there may especially be mentioned hydrochloric, hydrobromic, hydriodic, sulphuric, formic, malcic, fumaric, oxalic, ascorbic, citric, acetic, methanesulphonic, *p*-toluenesulphonic, lactic, succinic, benzoic, salicylic, acetylsalicylic, malic, tartaric, glutamic and aspartic acid.

Some of the compounds of the invention are listed in Table 1 below.

The compounds of the invention are useful in therapy in the treatment of circulatory complaints, especially cardio-vascular illnesses. Certain of them are hypo-lipidaemic agents and hypo-cholesterolaemic agents, certain of them are blood platelet anti-aggregation agents, and finally, others of them are simultaneously hypolipidaemic, hypo-cholesterolaemic and anti-aggregation agents, the property shared by all the compounds being a beneficial effect on circulatory complaints and in particular on cardio-vascular illnesses.

The invention includes within its scope therapeutic compositions comprising at least one compound of formula I as such or as one of its non-toxic addition salts in combination with a physiologically acceptable excipient.

TABLE I




| Example | Code No. | A | B | Alk | R | Melting point |
|---|---|---|---|---|---|---|
| 1 | — | S | O | $C(CH_3)_2CH_2$ | $NH(CH_2)_2OH$ | 50°C |
| 2(a) | CRL 40 238 | S | O | $C(CH_3)_2CH_2$ | $NH(CH_2)_2OH$ | 148°C |
| 3 | CRL 40 251 | S | O | $C(CH_3)_2$ | $CONH(CH_2)_2OH$ | 66°C |
| 4(b) | CRL 40 253 | S | O | $C(CH_3)_2$ | $CO_2(CH_2)_2S(CH_2)_{16}S(CH_2)_2O_2C$ | (c) |
| 5 | CRL 40 272 | O | S | $CH_2$ | $CONH(CH_2)_2OH$ | 98°C |
| 6 | CRL 40 274 | O | S | $CH_2CH_2$ | $NH(CH_2)_2OH$ | 67–68°C |
| 7 | CRL 40 276 | O | S | $C(CH_3)_2CH_2$ | OH | (c) |
| 8 | CRL 40 279 | O | S | $C(CH_3)_2CH_2$ | $NH(CH_2)_2OH$ | 50°C |
| 9 | CRL 40 293 | O | O | $CH_2CH_2$ | OH | 78°C |
| 10 | CRL 40 310 | O | O | $C(CH_3)_2CH_2$ | OH | (c) |
| 11 | CRL 40 312 | O | O | $C(CH_3)_2CH_2$ | $O-SO_2CH_3$ | 85°C |
| 12 | CRL 40 282 | O | S | $CH(CH_3)CH_2$ | OH | (c) |
| 13 | CRL 40 300 | O | O | $CH(CH_3)CH_2$ | OH | <50°C |
| 14 | CRL 40 332 | O | O | $CH_2C(CH_3)_2$ | OH | 55°C |

Notes: (a): This is the hydrochloride of Example 1
(b): This is a diester, namely 3,14-dithia-1,16-hexadecyl di-[4-(4-chlorophenylthio)-phenoxy isobutyrate]
(c): Oil

TABLE 1 (Continued)

| Example | Code No. | A | B | Alk | R | Melting point |
|---|---|---|---|---|---|---|
| 15(d) | CRL 40 317 | O | O | $CH_2CH_2$ | $NH_2$ | 215°C |
| 16 | – | O | O | $CH_2CH_2$ | $O-SO_2CH_3$ | 68°C |
| 17(d) | CRL 40 295 | O | O | $CH_2CH_2$ | $NHCH_2CH_2OH$ | 141°C |
| 18(d) | CRL 40 311 | O | O | $C(CH_3)_2CH_2$ | $NHCH_2CH_2OH$ | 133°C |
| 19 | – | O | O | $CH(CH_3)CH_2$ | $O-SO_2CH_3$ | 50°C |
| 20(d) | CRL 40 301 | O | O | $CH(CH_3)CH_2$ | $NHCH_2CH_2OH$ | 145°C |
| 21(d) | CRL 40 302 | O | O | $CH(CH_3)CH_2$ | $NHC(CH_3)_2CH_2OH$ | 125°C |
| 22 | CRL 40 283 | O | S | $CH(CH_3)CH_2$ | $NHCH_2CH_2OH$ | (e) |
| 23 | CRL 40 309 | O | O | $C(CH_3)_2$ | $CONHCH_2CH_2OH$ | 77°C |
| 24(d) | CRL 40 334 | O | O | $CH_2$ | $CONHCH_2CH_2N(C_2H_5)_2$ | 120°C |
| 25(d) | CRL 40 337 | O | O | $CH_2$ | $C(=NH)NHOH$ | 148°C(f) |
| 26(d) | CRL 40 338 | O | O | $CH_2$ | $C(=NH)NH_2$ | 166°C |
| 27(d) | CRL 40 322 | O | O | $CH_2$ | 2-$\Delta^2$-imidazolinyle | 166°C(g) |
| 6 bis (h) | – | O | S | $CH_2CH_2$ | OH | 61°C |

Notes: (c): oil
(d): hydrochloride
(e): the free base melts at 98°C
(f): the free base melts at 99°C
(g): the free base melts at 117°C
(h): described as an intermediate in Example 6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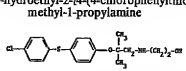
Other advantages and characteristics of the invention will be better understood on reading the preparation examples which follow and are given by way of illustration but without implying any limitation. In these examples, the synthesis of the compounds II, V and VI, which can be used as the starting material according to the invention, has also been illustrated. Furthermore, it is obvious that the isomers (+) and (–) of the racemic compounds which have been described in the said examples can be isolated, in accordance with a method which is in itself known.

Example 1.

N-Hydroxyethyl-4-(4-chlorophenylthio)-phenoxy-isobutylamine, alternative nomenclature: N-hydroethyl-2-[4-(4-chlorophenylthio)-phenoxyl-2-methyl-1-propylamine



A solution of 21.6 g (0.075 mol) of sodium bis-(2-methoxy-ethoxy)-aluminium hydride in 50 ml of benzene is run over the course of 30 minutes into a refluxing solution of 18.3 g (0.050 mol) of N-hydroxyethyl-4-(4-chlorophenylthio)-phenoxy-isobutyramide (prepared as indicated later in Example 7) in 75 ml of benzene. The mixture is kept under reflux for 1 hour 30 minutes and is then hydrolysed with 100 ml of 4 N sodium hydroxide solution, whilst cooling. The organic phase is decanted, washed with water and extracted with dilute hydrochloric acid, and after rendering the aqueous phase alkaline with concentrated sodium hydroxide solution, 10.6 g of an orange product are obtained.

Instantaneous melting point (Köfler)=50°C.

Example 2.

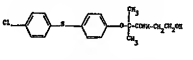
N-Hydroxyethyl-4-(4-chlorophenylthio)-phenoxy-isobutylamine hydrochloride Code No. CRL 40,238

10 g of the free base of Example 1, in ethyl acetate, are treated with a solution of hydrogen chloride in ether. After purification of the precipitate by recrystallisation from a mixture of ethyl acetate and ethanol (1:2), 8 g of a slightly beige powder which is insoluble in water are obtained.

Instantaneous melting point (Köfler)=148°C.

Example 3.

N-Hydroxyethyl-4-(4-chlorophenylthio)-phenoxy-isobutyramide, alternative nomenclature N-hydroxyethyl-2-[4-(4-chlorophenylthio)-phenoxyl-2-methyl-1-propionamide



Code No. CRL 40, 251

a) *p*-(*p*-Chlorophenylthio)-phenoxy-isobutyroyl chloride

A mixture of 15 g (0.0465 mol) of *p*-(*p*-chlorophenylthio)-phenoxy-isobutyric acid (CRL 40,201) and of 16.75 ml (0.232 mol) of thionyl chloride is heated to the reflux temperature for 10 minutes. After having taken up the reaction mixture in benzene, filtered the solution in the presence of charcoal and evaporated the solvent, 16 g of an orange-coloured oil are obtained.

Yield = about 100%.

b) CRL 40,251

A solution of 16 g (0.040 mol) of the preceding acid chloride in 25 ml of benzene is run over the course of 15 minutes into a suspension of 13.4 g (0.220 mol) of 2-aminoethanol in 30 ml of benzene at between 20 and 55°C. The reaction mixture is heated to the reflux temperature for 2 hours and is evaporated to dryness under reduced pressure. The residue is dissolved in ethyl acetate, which is washed successively with water, dilute hydrochloric acid and a solution of potassium carbonate. The oil obtained, after evaporation of the solvent, is purified

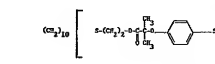
by washing in diisopropyl ether (sic), giving 10.6 g of a powder which is insoluble in water.

Instantaneous melting point (Köfler)=66°C.

Yield=62.8%.

Example 4.

3,14-Dithia-1,16-hexadecyl di[4-(4-chlorophenylthio)-phenoxyisobutyrate]



Code No. CRL 40,253

a) *p*-(*p*-Chlorophenylthio)-phenoxy-isobutyroyl chloride

A mixture of 15 g (0.0465 mol) of *p*-(*p*-chlorophenylthio)-phenoxy-isobutyric acid (CRL 40,201) and of 16.75 ml (0.232 mol) of thionyl chloride is heated to the reflux temperature for 10 minutes. After having taken up the reaction mixture in benzene, filtered the solution in the presence of carbon black and evaporated the solvent, 16 g of an orange-coloured oil are obtained.

Yield=about 100%.

b) CRL 40,253

A solution of 13 g (0.038 mol) of the preceding acid chloride in 25 ml of benzene is run over the course of 15 minutes into a suspension of 5 g (0.017 mol) of bis-1,10-(2-hydroxy-ethylthio)-decane in 20 ml of benzene and 3 g (0.038 mol) of pyridine at between 20 and 55°C. The reactants are left in contact overnight at ambient temperature and the reaction mixture is then washed with dilute hydrochloric acid. After drying over dry sodium sulphate and evaporating the solvent, 17.5 g of an orange-coloured oil are obtained. This oil is dissolved in diethyl ether and purified by 2 successive washes with potassium carbonate followed by dilute sodium hydroxide solution, giving 15.55 g of an orange-coloured oil which is insoluble in water.

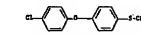
Yield=94%.

Preparation 1

On reacting ethyl α-bromoacetate with *p*-(*p*-chlorophenoxy)-thiophenol in accordance with the process described in Preparation 3 below, ethyl 4-(4-chlorophenoxy)-phenylthioacetate is obtained in the form of an oil.

Preparation 2

4-(4-Chlorophenoxy)-phenylthioacetic acid



Code No. CRL 40,271

Hydrolysis of the product of Preparation 1 in accordance with the working method described in Preparation 4 below gives 4-(4-chlorophenoxy)-phenylthioacetic acid.

Instantaneous melting point (Köfler)=87°C.

Example 5.

N-Hydroxyethyl-4-(4-chlorophenoxy)-phenylthioacetamide

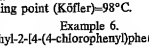
Code No. CRL 40,272

On subjecting the acid of Preparation 2 to an amidification reaction with 2-amino-ethanol in accordance with the working method described in Example 4, CRL 40,272 is obtained.

Instantaneous melting point (Köfler)=98°C.

Example 6.

N-Hydroxyethyl-2-[4-(4-chlorophenyl)phenylthio]-ethylamine



Code No. 40,274

a) 2-[4-(4-Chlorophenoxy)phenylthio]-ethanol (Example 12 bis)

3 ml (0.030 mol) of 10 N sodium hydroxide solution are run over the course of

10 minutes into a solution of 6.85 g (0.029 mol) of 4-(4-chlorophenoxy)-thiophenol and 2.58 g (0.32 mol) of 2-chloroethanol in 20 ml of ethanol, at between 20°C and 42°C. The mixture is stirred for 2 hours at ambient temperature and the solvent is then driven off under reduced pressure. After having dissolved the residue in diethyl ether, washed the organic phase obtained with dilute sodium hydroxide solution and water and then evaporated the solvent, 7.9 g of a fragrant pink powder are obtained. This powder is purified by crystallisation from cyclohexane to give 6.6 g of a pale pink powder.

Instantaneous melting point (Köfler)=61°C.

Yield=81.2%.

b) [4-(4-Chlorophenoxy)-phenylthio]-2-chloroethane

2 ml (0.0278 mol) of thionyl chloride are run over the course of 5 minutes into a solution of 6.5 g (0.0232 mol) of the preceding product in 15 ml of benzene and the mixture is then heated to the reflux temperature for 1 hour. The reaction mixture is then evaporated to dryness under reduced pressure and the residue is dissolved in diethyl ether. The organic phase obtained is washed with water and a potassium carbonate solution, dried over dry sodium sulphate and treated with charcoal, and the solvent is then evaporated to give 6.75 g of a white powder.

Instantaneous melting point (Köfler)=59°C.

Yield=97.2%.

c) CRL 40,274

A mixture of 6.7 g (0.224 mol) of the preceding product and of 6.85 g (0.112 mol) of 2-amino-ethanol is heated slowly to 170°C (over the course of 30 minutes). Thereafter the reaction mixture is taken up in chloroform and the chloroform solution is washed successively with water, dilute sodium hydroxide solution and water. After drying, and evaporating the solvent, 7.05 g of an oil which crystallises are obtained. 6.8 g of this product are purified by two successive crystallisations from diisopropyl ether to give 4.8 g of a white powder which is insoluble in water.

Instantaneous melting point (Köfler)=67—68°C.

Yield of stage c=70%.

Preparation 3

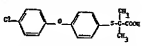
Ethyl 4-(4-chlorophenoxy)-phenylthio-isobutyrate, alternative nomenclature: ethyl 2-[4-(4-chlorophenoxy)-phenylthio]-2-methyl-propionate

9.05 g (0.0464 mol) of ethyl α-bromoisobutyrate are run over the course of 15 minutes, at about 60°C, into a solution of 10 g (0.0422 mol) of *p*-(*p*-chlorophenoxy)-thiophenol and 1 g (0.0422 mol) of sodium in 40 ml of anhydrous ethanol. The mixture is stirred for 1 hour at ambient temperature and is evaporated to dryness under reduced pressure. After having dissolved the residue in diethyl ether, and washed the organic phase obtained with water and dried it over dry sodium sulphate, the solvent is evaporated, to give 14.2 g of a limpid pale yellow oil.

Yield=96%.

Preparation 4

4-(4-chlorophenoxy)-phenylthio-isobutyric acid, alternative nomenclature: 2-[4-(4-chlorophenoxy)-phenylthio]-2-methylpropionic acid



Code No. CRL 40,275

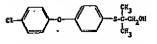
A solution of 14 g (0.04 mol) of the ester of Preparation 3 and of 3.36 g (0.06 mol) of potassium hydroxide pellets in 20 ml of water and 40 ml of ethanol is heated to the reflux temperature for 1 hour. The ethanol is evaporated under reduced pressure and the residue is diluted with 50 ml of water. The solution is acidified to Congo Red and the insoluble matter is extracted with diethyl ether. The organic phase obtained is in turn extracted with a potassium bicarbonate solution. After acidifying this aqueous phase with concentrated hydrochloric acid, 10 g of a white powder which is insoluble in water are isolated by extraction with diethyl ether.

Instantaneous melting point (Köfler)=131—132°C.

Yield=77.5%.

Example 7.

4-(4-Chlorophenoxy)-phenylthio-isobutanol, alternative nomenclature: 2-[4-(4-chlorophenoxy)-phenylthio]-2-methyl-1-propanol



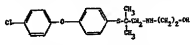
Code No. CRL 40,276

A solution of 9 g (0.0279 mol) of *p*-(*p*-chlorophenoxy)-phenylthio-isobutyric acid (CRL 40,275) in 75 ml of diethyl ether and 7.5 ml of tetrahydrofuran is run over the course of 30 minutes into a suspension of 2.4 g (0.0617 mol) of lithium aluminium hydride in 20 ml of diethyl ether and the mixture is then stirred for 1 hour at the reflux temperature. The excess hydride is neutralised with ethyl acetate and the product is hydrolysed with a dilute hydrochloric acid solution, whilst cooling. After washing the organic phase obtained with water and dilute sodium hydroxide solution, drying it and evaporating the solvent, 8.6 g of a limpid pale yellow oil are obtained.

Yield: about 100%.

Example 8.

N-Hydroxyethyl-4-(4-chlorophenoxy)phenylthio-isobutylamine, alternative nomenclature: N-hydroxyethyl-2-[4-(4-chlorophenoxy)-phenylthio]-2-mthyl-1-propylamine



Code No. CRL 40,279

2.25 ml (0.0311 mol) of thionyl chloride are run over the course of 5 minutes into a solution of 8 g (0.0259 mol) of *p*-(*p*-chlorophenoxy)-phenylthio-isobutanol (CRL 40,276) in 30 ml of anhydrous benzene and 0.5 ml of anhydrous pyridine. The mixture is heated to the reflux temperature for 30 minutes and is evaporated to dryness under reduced pressure. After dissolving the residue in diethyl ether, washing the ether solution with water and drying it over dry sodium sulphate, and evaporating the solvent, 8.05 g of 4-(4-chlorophenoxy)-phenylthio-isobutyl chloride are obtained in the form of a limpid orange-yellow oil.

Yield=95.2%.

A mixture of 8 g (0.024 mol) of the preceding product and 7.35 g (0.120 mol) of 2-amino-ethanol is gradually heated to 170° over the course of 30 minutes. The reaction mixture is taken up in diethyl ether, which is washed with water. The organic phase is extracted with a dilute hydrochloric acid solution, which is in turn rendered alkaline to permit the extraction of 6.85 g of a pale yellow oil which is insoluble in water and crystallises on cooling.

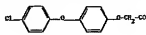
Melting point <50°C.

Yield=81.5%.

Total yield=77.5%.

Preparation 5

4-(4-Chlorophenoxy)-phenoxyacetic acid



Code No. CRL 40,333

a) *p*-Bromoanisole

25 g (0.20 mol) of dimethyl sulphate are run over the course of 45 minutes into a refluxing suspension of 34.4 g (0.20 mol) of *p*-bromophenol and 27.5 g (0.20 mol) of potassium carbonate in 150 ml of acetone. The reflux is maintained for a further hour, the inorganic salts are removed by filtration and the filtrate is evaporated to dryness, under reduced pressure. The residue is dissolved in diethyl ether, the ether solution is washed with dilute sodium hydroxide solution and water and is dried over dry sodium sulphate, and the solvent is evaporated to give 37.2 g of a slightly yellow oil which is insoluble in water.

Yield=99.5%.

Boiling point/13 mm Hg=95°C.

b) *p*-(*p*-Chlorophenoxy)-anisole

A mixture of 67 g (0.520 mol) of *p*-chlorophenol and 29.5 g (0.520 mol) of KOH pellets is heated to 100°C for 2 hours under a pressure of about 5 mm Hg. Thereafter 117 g (0.625 mol) of *p*-bromoanisole and 1 g of copper powder are added and the mixture is then heated to about 220—230°C for 5 hours. The cooled reaction mixture is taken up in diethyl ether and after removing the inorganic salts by filtration the filtrate is washed with 2 N sodium hydroxide solution and with water. The solvent is driven off under reduced pressure, drying is carried out with sodium sulphate and 133 g of an orange-coloured oil are obtained. Purification of this oil by distillation under reduced pressure gives 70 g of a white crystalline mass which is insoluble in water.

Boiling point/2—3 mm Hg=150°C.

Yield=57.3%.

c) *p*-(*p*-Chlorophenoxy)-phenol

A solution of 69 g (0.294 mol) of the preceding product and of 265 ml of 48% strength hydrobromic acid in 630 ml of acetic acid is heated to the reflux temperature for 2 hours and is then evaporated to dryness under reduced pressure. The residue is dissolved in diethyl ether, which is washed successively with water and a potassium bicarbonate solution. After drying over dry sodium sulphate and evaporating the solvent of the organic phase, 64.7 g of a slightly beige powder are obtained. Purification of this powder by crystallisation from cyclohexane gives 60.5 g of a white crystalline powder which is insoluble in water.

Instantaneous melting point (Köfler)=82°C.

Boiling point/0.4 mm Hg=143°C.

Yield=93.5%

d) CRL 40,333

A solution of 7.1 g (0.075 mol) of chloroacetic acid in 20 ml of ethanol is run over the course of 30 minutes into a solution, kept at about 60°C, of 15 g (0.068 mol) of the preceding product and 6.3 g (0.157 mol) of sodium hydroxide pellets in 50 ml of water. The mixture is heated to the reflux temperature for 2 hours, the ethanol is driven off under reduced pressure and the residue is acidified to Congo Red with dilute hydrochloric acid. The precipitate obtained is filtered off and dried. The purification of this precipitate by washing with hot diisopropyl ether gives 10 g of a slightly pink crystalline powder which is insoluble in water.

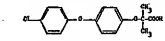
Instantaneous melting point (Köfler)=162°C.

Yield of stage d)=53%.

Total yield=21.2%.

Preparation 6.

4-(4-Chlorophenoxy)-phenoxy-isobutyric acid, alternative nomenclature: 2-[4-(4-chlorophenoxy)-phenoxyl-2-methylpropionic acid



Code No. CRL 40,308

17.5 ml (0.1530 mol) of chloroform are run (over the course of 30 minutes) into a hot suspension of 25.9 g (0.1175 mol) of *p*-(*p*-chlorophenoxy)-phenol and 28.2 g (0.7050 mol) of sodium hydroxide pellets in 152 ml (2.3500 mols) of acetone and the reflux is then maintained for 4 hours. The reaction mixture is evaporated to dryness under reduced pressure, the residue is taken up in water and the mixture is acidified to Congo Red with concentrated hydrochloric acid. The insoluble matter is extracted with diethyl ether and the organic phase is in turn extracted with a potassium bicarbonate solution. Acidification of the aqueous phase with concentrated hydrochloric acid liberates a precipitate which is isolated by filtration. Purification of this precipitate by two successive crystallisations and treatment with charcoal (CXA) in cyclohexane gives 25.6 g of a slightly yellow powder which is insoluble in water.

Instantaneous melting point (Köfler)=131°C.

Yield=74%.

Example 9.
2-[4-(4-Chlorophenoxy)-phenoxy]ethanol



Code No. CRL 40,293

6.6 g (0.082 mol) of 2-chloro-ethanol are run over the course of 5 minutes into a hot solution of 15 g (0.068 mol) of *p*-(*p*-chlorophenoxy)-phenol and 2.75 g (0.068 mol) of sodium hydroxide pellets in 40 ml of anhydrous ethanol. The mixture is heated to the reflux temperature for 4 hours, the inorganic salts are removed by filtration and the ethanol is driven off under reduced pressure. After having taken up the reaction mixture in diethyl ether, washed the organic phase thus obtained with 2 N sodium hydroxide solution and with water, dried it and evaporated the solvent, 11 g of pasty crystals are obtained.

10.5 g of these crystals are purified by crystallisation from diisopropyl ether to give 6.7 g of shiny white flakes.

Instantaneous melting point (Köfler)=78°C.

Yield=39%.

Example 10.
4-(4-Chlorophenoxy)-phenoxy-isobutanol, alternative nomenclature:
2-[4-(4-chlorophenoxy)phenoxy]-2-methyl-1-propanol

Code No. CRL 40,310

A solution of 12 g (0.0392 mol) of 4-(4-chlorophenoxy)phenoxy-isobutyric acid (CRL 40,308) in 80 ml of anhydrous diethyl ether and 2 ml of tetrahydrofuran is run over the course of 30 minutes into a suspension of 3.35 g (0.0883 mol) of LiAlH, in 30 ml of anhydrous diethyl ether and the reflux is then maintained for 1 hour 30 minutes. The excess hydride is neutralised with ethyl acetate and the complex is hydrolysed with a dilute hydrochloric acid solution. The organic phase is decanted and washed with water and dilute sodium hydroxide solution, and after drying and evaporation of the solvent gives 11.5 g of a thick yellow oil which is insoluble in water.

Yield about 100%.

Example 11.
4-(4-Chlorophenoxy)-phenoxy-isobutyl mesylate, alternative nomenclature:
2-[4-(4-chlorophenoxy)-phenoxy]-2-methylpropyl methanesulphonate



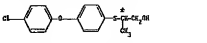
Code No. CRL 40,312

4.1 g (0.0356 mol) of methanesulphonyl chloride are run (over the course of 8 minutes) into a solution, kept at about 10°C, of 10.4 g (0.0356 mol) of 4-(4-chlorophenoxy)-phenoxy-isobutanol (CRL 40,310) in 17.5 ml of anhydrous pyridine, and the mixture is stirred for 1 hour at ambient temperature. The reaction mixture is poured onto ice and is acidified to Congo Red with concentrated hydrochloric acid. The insoluble matter is extracted with ethyl acetate and the organic phase thus obtained is washed with water, dried and evaporated to dryness under reduced pressure, to give 13.7 g of a yellow powder. The purification of this powder by crystallisation and treatment with charcoal (CXA) in diisopropyl ether gives 10.5 g of a white powder which is insoluble in water.

Instantaneous melting point (Köfler)=85°C.

Yield=78.3%.

Example 12.
(±)-2-[4-(4-Chlorophenoxy)-phenylthio]-1-propanol

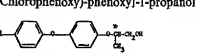


Code No. CRL 40,282

A solution of 9 g (0.292 mol) of (±)-2-[4-(4-chlorophenoxy)-phenylthio-propionic acid (CRL 40,281) in 75 ml of anhydrous diethyl ether and 2 ml of dried tetrahydrofuran is run over the course of 50 minutes into a suspension of 2.5 g (0.0656 mol) of $LiAlH_4$ in 20 ml of anhydrous diethyl ether. The mixture is heated to the reflux temperature for 1 hour, the excess hydride is destroyed with ethyl acetate and hydrolysis is carried out with a dilute hydrochloric acid solution. After washing the organic phase thus obtained with water and dilute sodium hydroxide solution, then drying it over dry sodium sulphate and evaporating the solvent, 8.6 g of a water-insoluble colourless oil having a yellow sheen is obtained.

Yield=about 100%.

Example 13.
(±)-2-[4-(4-Chlorophenoxy)-phenoxy]-1-propanol



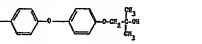
Code No. CRL 40,300

A solution of 22.5 g (0.077 mol) of (±)-2-[4-(4-chlorophenoxy)-phenoxy]-propionic acid (CRL 40299) in 150 ml of anhydrous diethyl ether is run over the course of 1 hour 30 minutes into a suspension of 6.6 g (0.173 mol) of $LiAlH_4$ in 50 ml of anhydrous diethyl ether. Thereafter the reflux is maintained for 1 hour 30 minutes, the excess hydride is neutralised with ethyl acetate and the complex is hydrolysed with dilute hydrochloric acid. The organic phase is decanted, washed with water and dilute sodium hydroxide solution and gives, after drying over dry sodium sulphate and evaporation of the solvent, 21.4 g of a crystalline white mass, which is insoluble in water.

Melting point ≤50°C.

Yield about 100%.

Example 14.
1-[4-(4-Chlorophenoxy)-phenoxy]-2-methyl-2-propanol



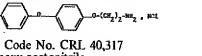
Code No. CRL 40,332

A solution of 8.15 g (0.075 mol) of 1-chloro-2-methyl-2-propanol in 20 ml of ethanol is run over the course of 25 minutes into a solution, kept at about 60°C, of 15 g (0.068 mol) of *p*-(*p*-chlorophenoxy)phenol and of 3 g (0.075 mol) of sodium hydroxide pellets in 20 ml of water and 20 ml of ethanol. The mixture is heated to the reflux temperature for 2 hours and the ethanol is driven off under reduced pressure. The residue is extracted with diethyl ether and after drying and evaporation of the solvent gives 7.3 g of a yellow oil. This oil is purified by crystallisation from a mixture of cyclohexane and petroleum ether (1:2 by volume) followed by washing with 2 N NaOH. 4 g of a white powder which is insoluble in water are obtained.

Instantaneous melting point (Köfler)=55°C.

Yield: 20.3%.

Example 15.
2-[4-(4-Chlorophenoxy)-phenoxy]-ethylamine hydrochloride



Code No. CRL 40,317

a) 4-(4-Chlorophenoxy)-phenoxy-acetonitrile

A solution of 3.78 g (0.0500 mol) of chloroacetonitrile in 10 ml of anhydrous .

ethanol is run over the course of 20 minutes into a solution of 1.04 g (0.0453 mol) of sodium and of 10 g (0.0453 mol) of *p*-(*p*-chlorophenoxy)-phenol in 50 ml of anhydrous ethanol and the mixture is then heated to the reflux temperature for 4 hours. It is evaporated to dryness under reduced pressure and the residue is dissolved in diethyl ether, which is washed with water and with dilute sodium hydroxide solution. After drying over dry sodium sulphate and evaporating the solvent from the organic phase, 12 g of an orange-coloured oil are obtained. Purification of this oil by distillation under reduced pressure gives 9.5 g of a limpid pale yellow oil which is insoluble in water.

Boiling point/0.4 mm Hg=165°C.
Yield=81%.

b) CRL 40,317

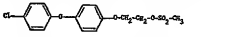
A solution of 9 g (0.0347 mol) of the preceding nitrile in 50 ml of anhydrous diethyl ether is run over the course of 50 minutes into a suspension of 3.3 g (0.0868 mol) of $LiAlH_4$ in 40 ml of anhydrous diethyl ether. The mixture is heated to the reflux temperature for 1 hour, the excess hydride is neutralised with ethyl acetate and the complex is then hydrolysed with dilute sodium hydroxide solution. The organic phase is decanted, washed with water, dried over sodium sulphate and evaporated to give 7.5 of a limpid pale yellow oil which crystallises.

4.5 of this product in diethyl ether are treated with a solution of hydrogen chloride in ether. After purification of the precipitate obtained, by crystallisation and treatment with CXA charcoal, in a mixture of isopropanol and cyclohexane (1:1 by volume), 2 g of a beige powder which is soluble in water are obtained.

Instantaneous melting point (Köfler)=215°C.
Yield of stage b)=21.4%.

## Example 16.

2-[4-(4-Chlorophenoxy)-phenoxy]-ethyl mesylate

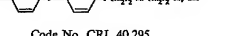


2.6 g (0.0227 mol) of methanesulphonyl chloride are run over the course of 5 minutes, at about +10°C, into a solution of 6 g (0.0227 mol) of 2-[4-(4-chlorophenoxy)-phenoxy]-1-ethanol (CRL 40,293) in 11 ml of pyridine and the mixture is then stirred for 1 hour at ambient temperature. Thereafter the reaction mixture is poured into ice and acidified to Congo Red with concentrated hydrochloric acid. After extracting the insoluble matter with ethyl acetate, washing the organic phase obtained with water and drying it over dry sodium sulphate, evaporation of the solvent gives 7.8 g of a white powder.

Instantaneous melting point (Köfler)=68°C.
Yield about 100%.

## Example 17.

N-Hydroxyethyl-2-[4-(4-chlorophenoxy)-phenoxy]-1-ethylamine hydrochloride



Code No. CRL 40,295

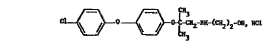
A mixture of 7.8 g (0.0227 mol) of the preceding product and of 13.8 g (0.2270 mol) of 2-aminoethanol is heated slowly to 170°C. The reaction mixture is allowed to return to ambient temperature and is taken up in water. After extracting the insoluble matter with diethyl ether, washing the extract with water, drying it and evaporating the solvent, 6.55 g of a white powder which is insoluble in water are obtained.

Instantaneous melting point (Köfler)=98°C.

6 g of this product, in ethyl acetate, are treated with a solution of hydrogen chloride in ether and the product is then purified by crystallisation from a mixture of ethanol and ethyl acetate (1:3 by volume), to give 5.6 g of a hydrochloride which is in the form of white flakes soluble in water to the extent of 200 g/l.

Instantaneous melting point (Köfler)=141°C.
Yield=77.5%.

Example 18.
N-Ethanol-2-[4-(4-chlorophenoxy)-phenoxy]-2-methyl-1-propylamine hydrochloride



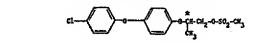
Code No. CRL 40,311

A solution of 7.8 g (0.0386 mol) of sodium bis-(2-methoxy-ethoxy)-aluminium hydride in 25 ml of benzene is run over the course of 45 minutes into a solution, at the reflux temperature, of 9 g (0.0257 mol) of N-ethanol-2-[4-(4-chlorophenoxy)-phenoxyl-2-methyl-1-propionamide (CRL 40,309), prepared as indicated in Example 23 below, in 40 ml of anhydrous benzene, and the reflux is maintained for a further 45 minutes. The complex is hydrolysed with dilute sodium hydroxide solution and the organic phase is decanted, washed with water and dried; evaporation of the solvent gives an orange-coloured oil.

This oil is treated with a solution of hydrogen chloride in diethyl ether, the precipitate obtained is isolated by filtration and the mother liquor is evaporated so as to recover the unreacted starting amide. Purification of the precipitate by a further conversion to the base and then to the salt, and by a crystallisation from a mixture of ethyl acetate and ethanol (1:1) in the presence of charcoal (CXA) gives 1.6 g of a white powder which is soluble in water.

Instantaneous melting point (Köfler)=133°C.

Example 19.
(±)-2-[4-(4-Chlorophenoxy)-phenoxyl-propyl mesylate

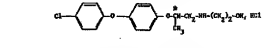


8.1 g (0.07 mol) of methanesulphonyl chloride are run, at about 10°C, into a solution of 19.5 g (0.07 mol) of (±)-2-[4-(4-chlorophenoxy)-phenoxyl-1-propanol (CRL 40,300) prepared as indicated in Example 13, in 35 ml of pyridine. The reaction mixture is stirred for 1 hour at ambient temperature and is poured onto ice. The insoluble matter is extracted with diethyl ether and the organic phase obtained is washed with dilute hydrochloric acid and dried, to give a white pasty residue after evaporation of the solvent. The solidification of this residue in petroleum ether gives 24 g of a white powder which is insoluble in water.

Melting point below 50°C.

Yield: 96.2%.

Example 20.
(±)-N-Hydroxyethyl-2-[4-(4-chlorophenoxy)-phenoxyl-1-propylamine hydrochloride



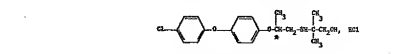
Code No. CRL 40,301

A mixture of 10 g (0.028 mol) of the mesylate of Example 19 and of 17 g (0.280 mol) of 2-aminoethanol is slowly heated to 170°C. The reaction mixture is allowed to return to ambient temperature and is taken up in water. After extracting the insoluble matter with diethyl ether, washing the organic phase with water and drying it over dry sodium sulphate, 8.7 g of a pale yellow oil are obtained after evaporation of the solvent. 8.4 g of this product, in ethyl acetate, are treated with a solution of hydrogen chloride in ether and the product is then purified by crystallisation from a mixture of ethyl acetate and anhydrous ethanol (7:2 by volume) to give 8.3 g of white flakes which are soluble in water to the extent of 200 g/l.

Instantaneous melting point (Köfler)=145°C.

Yield=86%.

Example 21.
(±)-N-(β-Hydroxy-α,α-dimethylethyl)-2-[4-(4-chlorophenoxy)-phenoxy]-1-propylamine hydrochloride



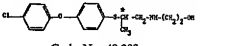
Code No. CRL 40,302

A mixture of 13 g (0.0365 mol) of the mesylate of Example 19 and of 32.5 g (0.365 mol) of 2-amino-2-methyl-1-propanol is heated slowly to 170°C. The reaction mixture is allowed to return to ambient temperature and is taken up in water. The insoluble matter is extracted with diethyl ether and the organic phase obtained is washed with water and dried over dry sodium sulphate to give, after evaporation of the solvent, 12.7 g of a limpid pale yellow oil. After treating 12 g of this oil in a solution of hydrogen chloride in diethyl ether, and purifying the product by crystallisation from ethyl acetate, 11.2 g of a white powder which is soluble in water to the extent of 200 g/l are obtained.

Instantaneous melting point (Köfler)=125°C.

Yield=84.2%.

Example 22.
(±)-N-Hydroxyethyl-2-[4-(4-chlorophenoxy)-phenylthio]-1-propylamine



Code No. 40,283

a) 2-Chloro-1-[4-(4-chlorophenoxy)-phenylthio]-propane

2.35 ml (0.0326 mol) of thionyl chloride are run, over the course of 7 minutes, into a solution of 8 g (0.0271 mol) of (±)-2-[4-(4-chlorophenoxy)-phenylthio]-1-propanol (CRL 40,282) prepared as indicated in Example 12 and of 0.5 ml of pyridine in 30 ml of anhydrous benzene. The reaction mixture is heated to the reflux temperature for 1 hour and is washed with water and with a potassium bicarbonate solution. After drying over dry sodium sulphate and evaporating the solvent, 8.05 g of a limpid pale yellow oil which is insoluble in water are obtained.

Yield 95%.

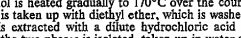
b) CRL 40,283

A mixture of 7.95 g (0.0254 mol) of the preceding product and of 7.75 g (0.1270 mol) of 2-aminoethanol is heated gradually to 170°C over the course of 1 hour. The reaction mixture is taken up with diethyl ether, which is washed with water. The aqueous phase is extracted with a dilute hydrochloric acid solution; the insoluble oil between the two phases is isolated, taken up in water and extracted with diethyl ether in the presence of potassium carbonate. After drying the organic phase over dry sodium sulphate, treating it with CXA charcoal, and evaporating the solvent, 7.8 g of a yellow oil are obtained. 6 g of this oil are purified by a further base/salt conversion to give 5.75 g of a pale yellow oil which is soluble in an aqueous hydrochloric acid solution at between pH 3 and pH 7.

Yield of stage b)=87.2%.

Total yield=83%.

Example 23.
N-Hydroxyethyl-2-[4-(4-chlorophenoxy)-phenoxy]-2-methylpropionamide



Code No. 40,309

a) 2-[4-(4-Chlorophenoxy)-phenoxy]-methyl-propionyl chloride

A mixture of 12 g (0.0392 mol) of 4-(4-chlorophenoxy)-phenoxy-isobutyric acid (CRL 40,308) prepared as described in Preparation 6, and of 14.15 ml (0.1960 mol) of thionyl chloride is heated to the reflux temperature for 50 minutes. The reaction mixture is taken up in benzene, the solution is filtered in the presence of CXA charcoal, and after having evaporated the solvent under reduced pressure 12.5 g of a brown-red oil are obtained.

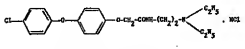
Yield=95.5%.

b) CRL 40,309

A solution of 12 g (0.0369 mol) of the preceding product in 40 ml of anhydrous benzene is run (over the course of 15 minutes), at between 20 and 36°C, into a suspension of 11.3 g (0.1850 mol) of ethanolamine in 30 ml of anhydrous benzene. The reaction mixture is heated to the reflux temperature for 1 hour and is then washed successively with water, dilute sodium hydroxide solution and a dilute hydrochloric acid solution. After drying over dry sodium sulphate, filtering, and evaporating the solvent from the organic phase, an orange-red crystalline mass is obtained. CRL 40,309 is purified by crystallisation, and treatment with CXA charcoal, in diisopropyl ether, to give 10.25 g of a slightly yellow powder which is insoluble in water.

Instantaneous melting point (Köfler)=77°C.
Yield of stage b)=79.5%.
Total yield=76%.

Example 24.
N-(2-Diethylaminoethyl)-4-(4-chlorophenoxy)-phenoxy-acetamide hydrochloride



Code No. CRL 40,334

a) 4-(4-Chlorophenoxy)-phenoxy-acetyl chloride

A mixture of 8.3 g (0.0298 mol) of 4-(4-chlorophenoxy)-phenoxy-acetic acid (CRL 40,333) prepared as indicated in Preparation 5 and of 10.8 ml (0.1500 mol) of thionyl chloride is heated to the reflux temperature for 30 minutes. After having taken up the reaction mixture in benzene and evaporated the solution to dryness under reduced pressure, 8.7 g of a beige powder are obtained.

Instantaneous melting point (Köfler)=64°C.
Yield=98.3%.

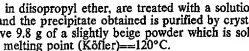
b) CRL 40,334

A solution of 8.5 g (0.0286 mol) of the preceding product in 20 ml of anhydrous benzene is run over the course of 15 minutes, at between 20°C and 40°C, into a solution of 16.6 g (0.1430 mol) of N,N-diethyl-ethylenediamine in 30 ml of anhydrous benzene. The reaction mixture is heated to the reflux temperature for 30 minutes and is then washed with water. After drying, and evaporating the solvent from the organic phase, 10.75 g of an orange-coloured oil are obtained.

9.5 g of this oil, in diisopropyl ether, are treated with a solution of hydrogen chloride in ether and the precipitate obtained is purified by crystallisation from ethyl acetate to give 9.8 g of a slightly beige powder which is soluble in water.

Instantaneous melting point (Köfler)=120°C.
Yield of stage b)=94.5%.
Total yield=93%.

Example 25.
4-(4-Chlorophenoxy)-phenoxy-acetamidoxime hydrochloride



Code No. CRL 40,337

A suspension of 5.37 g (0.0772 mol) of hydroxylamine hydrochloride and of 7.72 g (0.0772 mol) of potassium bicarbonate in 8 ml of water is added, all at once, to a suspension of 10 g (0.0385 mol) of 4-(4-chlorophenoxy)-phenoxy-acetonitrile prepared as indicated in Example 15a), in 24 ml of n-butanol. The mixture is heated to the reflux temperature for 1 hour, the butanol is driven off, the residue is taken up in water and the insoluble matter is extracted with diethyl ether. The organic phase is washed with water, dried over dry sodium sulphate and evaporated, and the residue obtained is purified by washing with hot diisopropyl ether to give 10 g of brilliant white needles.

Instantaneous melting point (Köfler)=99°C.

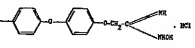
After treating 9.5 g of this product in a solution of hydrogen chloride in diethyl ether and purifying the product by crystallisation from isopropanol, 10.15 g of a white powder which is partially soluble in water are obtained.

Instantaneous melting point (Köfler)=148°C.

Yield=85%.

Example 26.

4-(4-Chlorophenoxy)-phenoxy-acetamidine hydrochloride



Code No. CRL 40,338

a) Ethyl 4-(4-chlorophenoxy)-phenoxy-acetimidate hydrochloride

A solution of 15 g (0.0578 mol) of 4-(4-chlorophenoxy)-phenoxy-acetonitrile prepared as indicated in Example 15a) and of 3.7 ml (0.0637 mol) of anhydrous ethanol in 75 ml of anhydrous diethyl ether is kept at about −5°C and a stream of dry hydrogen chloride gas is passed into it for 2 hours. Thereafter the reaction mixture is left for 4 hours at about 2°C and 19.25 g of a white powder are isolated by filtration.

Instantaneous melting point (Köfler) ≃148°C.

Yield=97.5%.

b) CRL 40,338

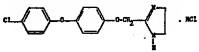
A stream of $NH_3$ is passed over the course of 1 hour at about 10°C into a solution of 10 g (0.0292 mol) of the preceding product in 100 ml of anhydrous ethanol. The reaction mixture is stirred for 4 hours at ambient temperature and is then evaporated to dryness under reduced pressure. After purifying the residue by washing it with diethyl ether, 8.55 g of a white powder are obtained. 7.55 g of this powder are again purified by a crystallisation and a treatment with CXA charcoal in isopropanol, to give 6.05 g of a white product which is soluble in water.

Instantaneous melting point (Köfler)=166°C.

Yield of stage b)=75.5%.

Example 27.

2-[4-(4-Chlorophenoxy)-phenoxy]-methyl-$\Delta^2$-imidazoline hydrochloride



Code No. CRL 40,322

A solution of 6 g (0.0175 mol) of the product of Example 26A) and of 1.25 ml (0.0184 mol) of ethylenediamine in 40 ml of anhydrous ethanol is heated to the reflux temperature for 2 hours 30 minutes. The ethanol is driven off under reduced pressure, the residue is taken up in dilute sodium hydroxide solution and the insoluble matter is extracted with diethyl ether. The product obtained after evaporation of the solvent is purified by washing it with diisopropyl ether, to give 4 g of a white powder which is insoluble in water.

Instantaneous melting point (Köfler)=117°C.

After treating 3.8 g of this powder, in ethyl acetate, with a solution of hydrogen chloride in ether, 3.8 g of a white powder which is soluble in hot water are obtained.

Instantaneous melting point (Köfler)=166°C.

Yield=80.5%.

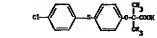
The examples which follow illustrate the production of a) addition salts with acids, and b) an ester from an acid of the formula I (R=COOH) and from a free base belonging to the group of bis-[(N-hydroxyalkyl)-amino-alkylthio]-alkanes of the formula:

$$Bo\text{-}NRo\text{-}Ao\text{-}SO_x\text{—}(CH_2)_n\text{—}SO_x\text{-}Ao\text{-}NRo\text{-}Bo$$

More precisely, the acids which were used are:
for Example 28, CRL 40,201, which is described in Preparation 7 below,
for Example 29, CRL 40,239 which is described in Preparation 8 below,
for Example 30, CRL 40,248 which is described in Preparation 9 below,
for Example 31, CRL 40,202 which is described in Prepartion 10 below, and for Example 32, CRL 40246 described in Preparation 9 below.

Preparation 7.

4-(4-Chlorophenylthio)-phenoxyisobutyric acid, alternative nomenclature: 2-[4-(4-chlorophenylthio)-phenoxyl-2-methylpropionic acid



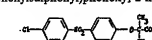
Code No. CRL 40,201

23.8 g (0.115 mol) of cuprous 4-chlorophenylthiolate (*p*-Cl—$C_6H_4$—S—Cu) are added to a solution of 28.7 g (0.1 mol) of ethyl 4-bromophenoxy-isobutyrate in 75 ml of quinoline and 25 ml of pyridine. The mixture is heated to 170°C whilst stirring for 3 hours. The solution is poured into ice containing 80 ml of concentrated HCl, the mixture is stirred for 1 hour and extracted with ethyl acetate, the extract is washed with water and then with dilute bicarbonate and is dried, and the ethyl acetate is driven off in vacuo. The oil thus obtained is dissolved in 120 ml of ethanol and is treated for 1 hour, at the reflux temperature, with 6 g (0.15 mol) of NaOH pellets in 75 ml of water. The ethanol is evaporated in vacuo, 200 ml of water are added to the residue and the acid is precipitated by means of concentrated HCl. It is filtered off, washed with water, dried and recystallised from diisopropyl ether. CRL 40,201 is obtained in a yield of 56%.

Melting point=146—148°C.

Preparation 8.

4-(4-Chlorophenylsulphonyl)-phenoxy-isobutyric acid, alternative nomenclature: 2-[4-(4-chlorophenylsulphonyl)phenoxy]-2-methyl-propionic acid



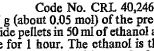
Code No. CRL 40,239

A solution of 10.75 g (0.033 mol) of *p*-(*p*-chlorophenylthio)-phenoxyisobutyric acid (CRL 40,201) and of 10 ml (0.100 mol) of hydrogen peroxide of 120 volumes strength, in 50 ml of acetic acid, is heated at between 55 and 70°C for 3 hours. Thereafter the greater part of the solvents is driven off under reduced pressure and the residue is dissolved in diethyl ether, which is washed with water. After evaporation of the solvent, the residual oil is solidified in petroleum ether and after filtration gives 10.7 g of a white powder which is insoluble in water and soluble in alcohol.

Instantaneous melting point (Köfler)=135°C.

Yield=91%.

Preparation 9.



Code No. CRL 40,246

A solution of 16.7 g (about 0.05 mol) of the preceding ester and of 3 g (0.075 mol) of sodium hydroxide pellets in 50 ml of ethanol and 25 ml of water is heated to the reflux temperature for 1 hour. The ethanol is then driven off under reduced pressure and the residue is diluted with 75 ml of water. The aqueous phase is acidified with hydrochloric acid and extracted with diethyl ether, and the extract is then washed with water. The organic phase is in turn extracted with a solution of potassium bicarbonate, and after acidification and filtration this aqueous phase gives 12.4 g of a slightly grey powder. After purification of 12 g of this powder by crystallisation, and treatment with charcoal, in diisopropyl ether, 8.2 g of a white powder which is insoluble in water and soluble in alcohol are obtained.

Instantaneous melting point (Köfler)=148°C.

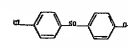
(Code No. CRL 40,248)

On oxidising the acid of Example 5 (CRL 40,246) by means of $H_2O_2$ as described in Example 3, (±)-2-[4-(4-chlorophenylsulphonyl)-phenoxyl-propionic acid is obtained.

Instantaneous melting point (Köfler)=178°C.

Preparation 10.

4-(4-Chlorophenylsulphinyl)-phenoxyisobutyric acid, alternative nomenclature: 2-[4-(4-chlorophenylsulphinyl)-phenoxyl-2-methyl-propionic acid



Code No. CRL 40,202

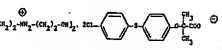
6.45 g (0.02 mol) of 4-(4-chlorophenylthio)-phenoxyisobutyric acid dissolved in 25 ml of acetic acid are oxidised with 2 ml (0.02 mol) of hydrogen peroxide of 110 volumes strength. The mixture is heated for 1 hour at 50°C and is evaporated to dryness in vacuo, and the residue is taken up in diisopropyl ether, filtered off and recystallised from ethyl acetate. This gives CRL 40,202 in a yield of 86%.

Melting point=140—142°C.

The free base used in Examples 28 to 32 is 6,17-dithia-3,20-diaza-1,22-docosanediol, which in the form of the dihydrochloride has been given Code No. LL 1,770.

Example 28.

6,17-Dithia-3,20-diaza-1,22-docosanediol di-*p*-(*p*-chlorophenylthio)-phenoxy-isobutyrate



Code No. CRL 40,240

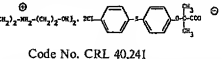
A hot solution of 6.45 g (0.02 mol) of *p*-(*p*-chlorophenylthio)-phenoxy-isobutyric acid in 25 ml of anhydrous ethanol is run into a hot solution of 3.8 g (0.01 mol) of 6,17-dithia-3,20-diaza-1,22-docosanediol (free base of LL 1,770) in 25 ml of anhydrous ethanol. The mixture is stirred for 2 hours at ambient temperature and the solvent is then evaporated under reduced pressure. After having washed the residue with acetonitrile, 8.4 g of a slightly beige powder which is insoluble in water but soluble in alcohol are obtained.

Instantaneous melting point (Köfler)=75°C.

Yield=82%.

Example 29.

6,17-Dithia-3,20-diaza-1,22-docosanediol di-*p*-(*p*-chlorophenylsulphonyl)-phenoxy-isobutyrate



Code No. CRL 40,241

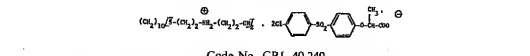
A hot solution of 6.6 g (0.0186 mol) of *p*-(*p*-chlorophenylsulphonyl)-phenoxy-isobutyric acid in 25 ml of anhydrous ethanol is run into a hot solution of 3.54 g (0.0093 mol) of 6,17-dithia-3,20-diaza-1,22-docosanediol in 25 ml of anhydrous ethanol. The mixture is stirred for 2 hours at ambient temperature and the solvent is then evaporated under reduced pressure. After having washed the residue with acetonitrile, 9.9 g of a slightly pink powder which is insoluble in water and soluble in hot alcohol are obtained.

Instantaneous melting point (Köfler)=137°C.

Yield=98%.

Example 30.

6,17-Dithia-3,20-diaza-1,22-docosanediol di-(±)-2-[p-(p-chlorophenyl-sulphonyl)-phenoxy]-propionate



Code No. CRL 40,249

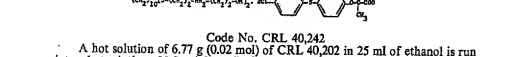
A hot solution of 5.10 g (0.0150 mol) of (±)-2-[p-(p-chlorophenylsulphonyl)-phenoxy]-propionic acid in 20 ml of anhydrous ethanol is run into a hot solution of 2.84 g (0.0075 mol) of 6,17-dithia-3,20-diaza-1,22-docosanediol (free base of LL 1,770) in 20 ml of anhydrous ethanol. After having left the reactants in contact for 15 minutes the solvent is evaporated under reduced pressure. The crystalline residue is then washed with acetonitrile to give 7.8 g of a white powder which is insoluble in water and in alcohol.

Instantaneous melting point (Köfler)=149—150°C.

Yield: 98.3%.

Example 31.

6,17-Dithia-3,20-diaza-1,22-docosanediol di-[4-(4-chlorosulphinyl)-phenoxy-isobutyrate]



Code No. CRL 40,242

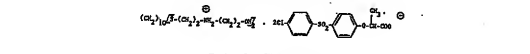
A hot solution of 6.77 g (0.02 mol) of CRL 40,202 in 25 ml of ethanol is run into a hot solution of 3.8 g (0.01 mol) of 6,17-dithia-3,20-diaza-1,22-docosanediol in 25 ml of ethanol. The mixture is stirred for 30 minutes at ambient temperature and the solvent is then evaporated under reduced pressure. After having solidified the residue in diisopropyl ether, 10.4 g of a white powder which is insoluble in water and soluble in alcohol are obtained.

Instantaneous melting point (Köfler)=about 85°C.

Yield=98.5%.

Example 32.

6,17-Dithia-3,20-diaza-1,22-docosanediol di-(±)-[2-(4-chlorophenylthio)-phenoxy-propionate]



Code No. CRL 40,247

A hot solution of 4.62 g (0.015 mol) of CRL 40,246 in 20 ml of anhydrous ethanol is run into a hot solution of 2.84 g (0.0075 mol) of 6,17-dithia-3,20-diaza-1,22-docosanediol in 20 ml of anhydrous ethanol. After having left the reactants in contact for 15 minutes, the solvent is evaporated under reduced pressure. The residue is then solidified in acetonitrile to give 7.2 g of a white powder which is insoluble in water and soluble in alcohol.

Instantaneous melting point (Köfler)=about 70°C.

Yield=96.5%.

The results of the pharmacological tests which were undertaken both in respect of the hypo-lipidaemic properties and hypo-cholesterolaemic properties, on the one hand, and of the anti-aggregation properties, on the other, have been summarised below.

The hypo-lipidaemic action and hypo-cholesterolaemic action have been demonstrated by studying various batches of Wistar rats:

A. a batch of rats receiving a normal diet (percentage inhibition=100%);

B. a batch of rats receiving a hyper-lipid diet (percentage inhibition=0%);

C. a batch of rats receiving the hyper-lipid diet B with a daily dose, of 0.1 g/kg, of a reference product having a lipidaemia-normalising action, namely Lipavlon [ethyl w-(p-chlorophenoxy)-2-methyl-propionate];

D. a batch of rats receiving the hyper-lipid diet B with a daily dose, of 0.1 g/kg, of another product having a lipidaemia-normalising action, namely LL 1558 [1,10-bis-(2-hydroxyethyl-thio)-decane]; and

E. a batch of rats receiving the hyper-lipid diet B with a daily dose of 10 mg/kg and 25 mg/kg and, where necessary, higher doses.

The anti-aggregation action has been demonstrated by studying the parameters which characterise the curve for the aggregation of platelets induced;

a) by collagen: the inhibition of aggregation (which corresponds to the % transmission), the latency period and the speed; and

b) the ADP: the inhibition of aggregation (that is to say the % transmission).

In Table II which follows have been shown the results relating to the anti-aggregation action of some products on the blood of male Wistar rats, the aggregating agents used being collagen/acetic acid diluted 1/10, and ADP at 1 $\mu$M.

TABLE II

| Example | Code No. | Oral dose, mg/kg | Duration of the treatment | Change in aggregation | | | |
|---|---|---|---|---|---|---|---|
| | | | | Collagen | | | ADP transmission |
| | | | | Latency period | Speed | Transmission | |
| 2 | CRL 40,238 | 100 | 4 days | +18% | -52% | -47% | -46% |
| 3 | CRL 40,251 | 200 | 4 days | +23% | -21% | - 5% | - 4% |
| 5 | CRL 40,272 | 100 | 4 days | -16% | - 7% | 0% | -20% |
| 6 | CRL 40,274 | 100 | 4 days | + 5% | 0% | - 3% | -20% |

The results of Table II show that the products studied are anti-aggregation agents, the most interesting amongst them being CRL 40,238 (Example 2).

The results of the anti-aggregation test and of the hypo-lipidaemic action and hypo-cholesterolaemic action tests of other products of the invention have been listed in Table III which follows, the code used being the following (for each dose shown):

zero activity : –

significant activity : +

intense activity : ++

very intense activity : +++

TABLE III

| Example | Code No. | Oral daily test dose in rats | Anti-aggregation action | Hypo-lipidaemic and hypo-cholesterolaemic action |
|---|---|---|---|---|
| 4 | CRL 40,253 | 10 mg/kg for 4 days | not tested | Total lipids: –40%<br>Cholesterol: –40% |
| 9 | CRL 40,293 | 50 mg/kg for 3 days | ++ (a) | Total lipids: 40%<br>Cholesterol: 40% |
| 10 | CRL 40,130 | 100 mg/kg for 4 days | – | Total lipids: –20%<br>Cholesterol: –32% |
| 11 | CRL 40,312 | 100 mg/kg for 4 days | + | – |
| 12 | CRL 40,282 | 100 mg/kg for 4 days | + | – |
| 13 | CRL 40,300 | 100 mg/kg for 4 days | + | – |
| 14 | CRL 40,282 | 100 mg/kg for 4 days | + | – |
| 15 | CRL 40,317 | 100 mg/kg for 4 days | + | Total lipids: –37%<br>Cholesterol: –58% |
| 17 | CRL 40,295 | 100 mg/kg for 4 days | +++ | Total lipids: –19%<br>Cholesterol: –32% |
| 17 | CRL 40,295 | 200 mg/kg for 4 days | +++ | Total lipids: –28%<br>Cholesterol: –37% |
| 22 | CRL 40,283 | 200 mg/kg for 4 days | + | not tested |
| 24 | CRL 40,334 | 100 mg/kg for 4 days | +++ | Total lipids: –17%<br>Cholesterol: –17% |
| 27 | CRL 40,322 | 100 mg/kg for 4 days | + | – |
| Note: (a): +++ at a dose of 100 mg/kg per day for 3 days | | | | |

The other pharmacological tests which have been carried out with CRL 40,293 (Example 9) have been listed below.

*Toxicity*

In female mice, the LD—50 on oral administration is 2,050 mg/kg. In male rats, the LD—0, on oral administration, is greater than 600 mg/kg.

It has furthermore been observed that CRL 40,293 is a well-tolerated substance. In fasting rats (a batch of 3 animals) which receive 1 g/kg of the product through a probang, no ulceration or inflammation of the stomach and of the duodenum is observed after killing the animals 8 hours after administration.

*Cardio-vascular activity*

Three anaesthetised dogs are used for this study. The product is administered intraduodenally as a gum suspension.

Two dogs with the thorax closed and respiring spontaneously are given CRL 40,293 at a dose of 100 mg/kg followed by 200 mg/kg, this second dose being administered 1 hour 30 minutes to 2 hours after the first. None of the parameters measured changed during the 2 hours' observation (arterial pressure, pulse rate, left intra-ventricular pressure, dp/dt, vertebral and femoral arterial flow rates and respiration).

One dog with the thorax opened is given 100 mg/kg, followed after 1 hour by 200 mg/kg, of CRL 40,293. None of the parameters measured changed during the 2 hours' observation (arterial pressure, pulse rate, left intra-ventricular pressure, dp/dt, aorta flow rate, work of the left ventricle, coronary arterial flow rate).

In these animals the effects of injections of noradrenalin, acetylcholine, tyramine, DMPP, histamine and serotonine were unchanged and the same is true of the effects of occlusion of the carotids and of stimulation of the central end and peripheral end of the vagus.

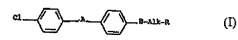
The product has a good hypo-lipidaemic and hypo-cholesterolaemic activity as indicated in Table III for an oral dose of 50 mg/kg. Furthermore, at a daily oral dose of 10 mg/kg the decrease in total lipids and in cholesterol is 20% after 3—4 days' treatment.

The clinical tests have made it possible to confirm the pharmacological tests. Thus, in man, CRL 40,293 (Example 9) in the form of gelatine-coated pills containing 400 mg of active ingredient administered at the rate of 2 such pills twice daily has given good results in the treatment of circulatory complaints and especially of lipid disturbances.

CRL 40,317 (Example 15) and CRL 40,295 (Example 17) each in the form of a tablet containing 250 to 500 mg of active ingredient, and administered to man to prevent cardiovascular accidents, were well tolerated, especially in the treatment of coronary insufficiency.

WHAT WE CLAIM IS:—

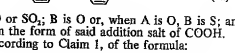
1. A diaryl compound of the general formula



(I)

in which one of A and B is O, S, SO or $SO_2$ and the other is O; Alk is a $C_1$—$C_4$ hydrocarbon radical with a straight or branched chain; R represents a group of formula COOX, wherein X is an esterified bis-[(S-hydroxyalkyl)thio]-alkane group, COOH in the form of its addition salt with a bis-[(N-hydroxyalkyl)amino-alkylthio]-alkane of the formula Bo-NRo-Ao-$SO_n$—$(CH_2)_x$—$SO_n$-Ao-NRo-Bo (IX), (wherein Bo is a $C_2$—$C_4$ hydroxyalkyl group or a $C_3$—$C_4$ dihydroxyalkyl group, Ao is a $C_2$—$C_6$ alkylene group, Ro is H, alkyl, acyl, or Bo, and x is 0, 1 or 2), OH, O—$SO_2CH_3$, $NH_2$, NHZOH, $NHZNR_1R_2$, C(=NH)$NH_2$, C(=NH)NHOH or $s\Delta^2$-imidazolinyl; Z is a $C_2$—$C_4$ hydrocarbon radical with a straight or branched chain; and $R_1$ and $R_2$ each represent a $C_1$—$C_4$ lower alkyl group, or together form, with the nitrogen atom to which they are linked, a N-heterocyclic group of 5 to 7 ring atoms which can be substituted and can comprise a second hetero-atom, and its addition salts with acids when R is a basic radical.

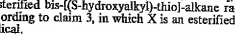
2. A compound according to Claim 1, of the formula:



(Ia)

in which A is O, S, SO or $SO_2$; B is O or, when A is O, B is S; and Y is $CH_2$, $CH(CH_3)$ or $C(CH_3)_2$; in the form of said addition salt of COOH.

3. A compound according to Claim 1, of the formula:

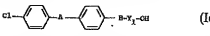


(Ib)

in which A is O, S, SO or $SO_2$; B is O or, when A is O, B is S; Y is $CH_2$, $CH(CH_3)$ or $C(CH_3)_2$; and X is an esterified bis-[(S-hydroxyalkyl)-thio]-alkane radical.

4. A compound according to claim 3, in which X is an esterified 3,14-dithia-1,16-hexadecanediol radical.

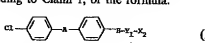
5. A compound according to Claim 1, of the formula:



(Ic)

in which A is O, S, SO or $SO_2$; B is O or, when A is O, B is S; and $Y_1$ is $CH_2CH_2$, $CH(CH_3)CH_2$, $C(CH_3)_2CH_2$, $CH_2CH(CH_3)$ or $CH_2C(CH_3)_2$; and its derivatives in which the OH group has been replaced by the $O—SO_2—CH_3$ group.

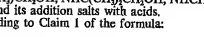
6. A compound according to Claim 1, of the formula:



(Id)

in which A is O, S, SO or $SO_2$; B is O or, when A is O, B is S; Y, is $CH_2CH_2$, $CH(CH_3)CH_2$, $C(CH_3)_2CH_2$, $CH_2CH(CH_3)$ or $CH_2C(CH_3)_2$; and $X_2$ is $NH_2$, $NHCH_2CH_2OH$, $NHCH(CH_3)CH_2OH$, $NHC(CH_3)_2CH_2OH$, $NHCH_2CH_2N(CH_3)_2$, or $NHCH_2CH_2N(C_2H_5)_2$; and its addition salts with acids.

7. A compound according to Claim 1 of the formula:



(Ie)

in which A is O, S, SO or $SO_2$, B is O or, when A is O, B is S; Y is $CH_2$, $CH(CH_3)$, or $C(CH_3)_2$; and $X_3$ is $C(=NH)NH_2$, $C(=NH)NHOH$ or 2-$\Delta^2$-imidazolinyl; and its addition salts with acids.

8. 3,14 - Dithia - 1,16 - hexadecyl di - [4 - (4 - chlorophenylthio) - phenoxy - isobutyrate].

9. 2-[4-(4-Chlorophenoxy)-phenoxy]-ethanol.

10. N - Hydroxyethyl - 2 - [4 - (4 - chlorophenoxy) - phenoxy] - ethylamine and its addition salts with acids.

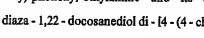
11. 2-[4-(4-Chlorophenoxy)-phenoxy]-ethylamine and its addition salts with acids.

12. 6,17 - Dithia - 3,20 - diaza - 1,22 - docosanediol di - [4 - (4 - chlorosulphinyl)-phenoxy-isobutyrate].

13. 3,20 - Di - [4 - (4 - chlorophenylthio) - phenoxyisobutyryl - 6,17 - dithia-3,20-diaza-1,22-docosanediol.

14. A therapeutic composition comprising at least one compound according to any one of Claims 1 to 13 as such or as a non-toxic addition salt thereof, in combination with a physiologically acceptable excipient.

15. A process for the preparation of a compound or salt according to Claim 1, which comprises reacting a diphenyl derivative of the formula:

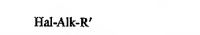


(II)

in which A and B are as defined in Claim 1, with a halogen compound of the formula:

Hal-Alk-R' (III)

in which Alk is as defined in Claim 1, Hal represents bromine or chlorine, and R' is $COOC_2H_5$, OH, $NH_2$, NHZOH, $NHZNR_1R_2$, or CN to produce a compound of the formula:



(IV)

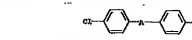
followed by:

(a) hydrolysing a carboxylate (IV, R'=$COOC_2H_5$) to the corresponding acid (R=COOH) which is then converted (by methods known *per se* into said COOX group or said addition salt of COOH, or is amidified and reduced to produce an amine; or followed by, if desired,

(b) converting an alcohol (IV, R'=OH) into the corresponding mesylate (R=$OSO_2CH_3$) by reaction with methane-sulphonyl chloride; or

(c) reacting a cyanide (IV, R'=CN) with $NH_2$, $NH_2OH$ or $H_2NCH_2CH_2NH_2$ in the presence of an alcohol to produce an amidino compound in which R is $C(=NH)NH_2$, $C(=NH)NHOH$, or 2-$A^2$-imidazolinyl, respectively.

16. A process for the preparation of a salt according to claim 2, which comprises reacting a compound of the formula:

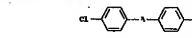


wherein A and B are as defined in Claim 2, with a bromo compound of the formula:

$$Br—Y—COOC_2H_5$$

wherein Y is as defined in Claim 2, hydrolysing the ester obtained, and converting (by methods known *per se*) the resulting acid to the specified addition salt of COOH.

17. A process for the preparation of a compound or salt according to Claim 6, which comprises reacting a diphenyl derivative of the formula:



wherein A and B are as defined in Claim 6, with a chloroalkylamine of the formula:

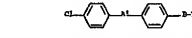
$$Cl—Y_1—X_2$$

wherein $Y_1$ and $X_2$ are as defined in Claim 6.

18. Process for the preparation of a compound or salt according to Claim 1, which comprises reacting a copper salt of formula:

where A' is O or S, with a bromo-compound of formula:

in which B is O or, when A' is O, B is S, and Y is $CH_2$, $CH(CH_3)$ or $C(CH_3)_2$, to produce an ester of the formula:



hydrolysing this ester to produce the corresponding acid, and reducing this acid to the corresponding alcohol, with or without converting the said alcohol into the mesylate by reaction with $CH_3OSO_2Cl$, esterifying the said acid to give the COOX ester, specified in Claim 1, amidifying said acid to produce an amide and reducing the amide to give an amine, and/or oxidising a sulphide atom to a sulphinyl or sulphonyl group with $H_2O_2$.

19. A process for the production of a compound as claimed in any of Claims 1 to 13 substantially as described in any one of the foregoing Examples.

20. A compound as claimed in any one of Claims 1 to 13 when produced by a process claimed in any one of Claims 15 to 19.

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Printed for Her Majesty's Stationery Office by the Courier Press, Leamington Spa, 1978.
Published by the Patent Office, 25 Southampton Buildings, London, WC2A 1AY, from which copies may be obtained.